REMARKS/ARGUMENTS

The abstract of the disclosure has been amended to shorten its length. No new matter has been added.

Claims 1-41 are pending in this application. Claims 3-4, 16-26, 29, 31-34 and 36-41 have been withdrawn by the Examiner as being drawn to non-elected inventions. Claims 10-14 and 20 have been amended to more particularly point out and distinctly claim certain embodiments of the present invention. No new matter has been added.

I. THE OBJECTION TO THE SPECIFICATION SHOULD BE WITHDRAWN

The abstract of the disclosure is objected to because it exceeds 150 words. In response, Applicant has amended the abstract so it does not exceed 150 words in length, as required by 37 C.F.R. § 1.72. As such, the objection is obviated and should be withdrawn.

II. THE CLAIM REJECTIONS UNDER 35 U.S.C. § 112 SHOULD BE WITHDRAWN

Claims 1-2, 5-15, 27-28, 30 and 35 are rejected under 35 U.S.C. § 112, first paragraph (Section § 112, ¶1), as allegedly failing to comply with the enablement requirement with respect to the elected invention and elected species. For the following reasons, Applicant respectfully disagrees.

1. The Legal Standard

The enablement requirement refers to the requirement of 35 U.S.C. § 112, first paragraph, that the specification describes (1) how to make and (2) how to use the invention. *See* MPEP § 2164. The test for enablement is whether one reasonably skilled in the art could make or use the invention, without undue experimentation, from the disclosure in the patent specification coupled with information known in the art at the time the patent application was filed. *United States v. Telectronics Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988). Enablement is not precluded even if some experimentation is necessary. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983).

By definition, undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. *Fields v. Conover,* 443 F.2d 1386, 1392, 170 USPQ 276, 279 (CCPA 1971). The factors that are relevant in

determining what constitutes undue experimentation as set forth by the Federal Circuit (citing *Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986)) include: "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." Any conclusion of nonenablement must be based on the evidence as a whole, and not based on an analysis of only one of the factors while ignoring one or more of the others. *In re Wands*, 858 F.2d 731, 740, 8 USPQ2d 1400, 1406 (Fed. Cir. 1988).

The Patent Office must establish a *prima facie* case of non-enablement in order to properly reject a claim on that basis. "When rejecting a claim under the enablement requirement of § 112, the Patent Office bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention in the specification of the application..." *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). The Patent Office's *prima facie* case should address each of the *Wands* factors since "[i]t is improper to conclude that a disclosure is not enabling based on an analysis of only one of the [*Wands*] factors while ignoring one or more of the others." *See* MPEP § 2164.01(a), citing *Wands* at 1407. Where the Patent Office does not provide evidence regarding one or more *Wands* factors, Applicant presumes that such factors support the conclusion that the claims at issue are fully enabled.

2. The Specification Enables the Methods of the Present Invention

The instant specification fully enables one of skill in the art to make and use the invention commensurate in scope with the claims without undue experimentation as explained below. In particular, Applicant submits that one skilled in the art, by using the teaching from the specification coupled with information known in the art, can make and use the invention, including (a) *in vivo* and *in situ* conditioning bone marrow from a human using a genetic engineering or a biological process (*e.g.*, transfecting the human bone marrow with a nucleic acid that encodes VEGF) to produce VEGF in an amount different than the amount of VEGF that the human bone marrow would produce absent the conditioning; (b) allowing the conditioned bone marrow to produce VEGF; (c) harvesting the conditioned bone marrow from the human; and (d) decellularizing the conditioned bone marrow to obtain an

extracellular matrix material containing VEGF, as recited in the elected invention and elected species.

As a preliminary matter, Applicant respectfully submits that the Examiner has not made an enablement rejection over the invention as defined by the claims. "The invention that one skilled in the art must be enabled to make and use is *that defined by the claim(s)* of the particular application or patent." *See* MPEP § 2164 (emphasis added). The Examiner alleges that "the sole purpose for a method of producing a decellularized extracellular matrix material containing a biological material is for treatment purpose in repairing, regenerating or strengthening tissue or organs *in vivo*," and then cites to several references that discusses the current state of gene therapy. *See* Office action, pages 4-5. However, none of independent claims 1, 27 and 35, or dependent claims thereof, as well as any of the withdrawn claims, are limited only to a method of treatment using gene therapy. Apparently, the rationale behind the Examiner's rejection is based on the position that just because the product of the claimed method can be used for gene therapy, that the method of making claims are somehow solely method of treatment claims involving gene therapy.

Independent claims 1 and 27 are directed to methods for producing a decellularized extracellular matrix material containing a biological material, and independent claim 35 is directed to methods of using the decellularized extracellular matrix material to form a tissue regeneration scaffold. The present invention is not directed solely to gene therapy, which "involves the transfer of genetic material into a cell, tissue, or whole organ, *with the goal of curing a disease or at least improving the clinical status of a patient.*"[1] Although the conditioning step of the claimed methods might involve the transferring of a genetic material into a tissue, the primary purpose and consequence of said genetic transfer is for inducing and/or altering gene product expression, not for the goal of curing a disease or at least improving the clinical status of a patient," as required for gene therapy. In fact, any therapeutic objectives based on the presently claimed invention involves the transferring of the decellularized extracellular matrix material containing the biological material into a cell, tissue, or organ, and not the transferring of the genetic material itself, as required by gene therapy, to a patient for treating a condition. Contrary to the Examiner's allegation, the sole purpose of the claimed method is not for use in gene therapy. Nor are the claimed methods directed to a type of gene therapy. As such, Applicant respectfully submits that the

Examiner's enablement rejection is based on an incorrect reading of the claimed methods of making and their application.

Nevertheless, the Examiner analyzed three *Wand* factors under the test for undue experimentation. First, the Examiner alleges that at the filing date of the present application, "the attainment of any therapeutic effect in any patient via gene therapy was, and remain highly unpredictable." *See* Office action, page 5. As already discussed, the invention as defined by the claims is not directed to gene therapy. Thus, the Examiner's discussion of the level of predictability in the art of gene therapy is irrelevant to the presently claimed invention.

Second, the Examiner alleges that the instant specification fails to provide any guidance for a skilled artisan on how to overcome the hurdle of *in vivo* vector targeting by any route of delivery and/or at any site in the human donor so that an efficient gene delivery can be attained in the human bone marrow tissue. *See* Office action, page 6.

Contrary to the Examiner's allegation, the specification is not absent in guidance or direction. Rather, the specification clearly teaches and fully describes ways to practice the claimed invention, specifically, the specification describes many ways of transfecting a body tissue with a nucleic acid that encodes a biological material of interest (see specification, *e.g.*, Section 4.1.2.1 at pages 14-20). In addition, the specification clearly teaches and fully describes how to culture the conditioned body tissue and monitor the effects of conditioning (see specification, *e.g.*, Sections 4.1.3 and 4.1.4 at pages 24-25), how to decellularize the conditioned body tissue (see specification, *e.g.*, Section 4.1.5 at pages 26-30), and how to make a tissue regeneration scaffold from the decellularized extracellular matrix material (see specification, *e.g.*, Section 4.2.3 at page 35). The amount of direction and guidance presented in the specification is more than sufficient. Applicant submits that based on the teachings of the specification and information known in the art, one skilled in the art would know how to *in vivo* or *in situ* condition human bone marrow by genetic engineering or a biological conditioning process (step (a) of claims 1, 27 and 35), culture the conditioned human bone marrow and determine the extent of culturing (step (b) of claims 1, 27 and 35), harvest the conditioned human bone marrow (step (c) of claims 1, 27 and 35), decellularize the conditioned human bone marrow (step (c) of claims 1, 27 and 35), and form a tissue regeneration scaffold (step (e) of claim 35). As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the

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[1] Verma *et al.*, "Gene Therapy: Twenty-First Century Medicine." Ann Rev. Biochem. 2005;74:711-38 (emphasis added).

entire scope of the claim, then the enablement requirement of Section § 112, ¶1, is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (emphasis added).

Finally, the Examiner alleges that there is an absence of an example demonstrating that any therapeutic effect has been attained or achieved for a genetically modified and acellular human bone marrow extracellular matrix produced by the elected invention. *See* Office action, page 7. As discussed above, the claims are not directed to gene therapy. Thus, the gene therapy-type example required by the Examiner is not relevant to whether the presently claimed invention is enabled. Accordingly, the Examiner's application of this *Wand* factor is again in error.

Furthermore, Applicant submits that the specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970). At most, the claims only relate to the use of gene delivery, which is one component of gene therapy, for the production of a biological material in a body tissue. Gene delivery is a well established art that is discussed extensively in the specification (see specification, *e.g.*, Section 4.1.2.1 at pages 14-20). The absence of an illustrative examples is not determinant on whether undue experimentation is required. *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971).

Applicant submits that when all of the *Wands* factors are considered, one of ordinary skill in the art can determine without undue experimentation how to make and use the presently claimed methods. Applicant submits that in view of the present specification and the knowledge in the art, the skilled artisan will be able to make a decellularized extracellular matrix material containing a biological material using, for example, a vector to transfect the human bone marrow with a nucleic acid that encodes VEGF. Moreover, Applicant submits that in view of the present specification and the knowledge in the art, the skilled artisan will also be able to use the decellularized extracellular matrix material, for example, to produce the claimed regeneration tissue scaffold. If a statement of utility in the specification contains within it a connotation of how to use, the enablement requirement of how to use under 35 U.S.C. § 112 is satisfied. *In re Johnson*, 282 F.2d 370, 373, 127 USPQ 216, 219 (CCPA 1960); *In re Hitchings*, 342 F.2d 80, 87, 144 USPQ 637, 643 (CCPA 1965). Accordingly, the instant specification fully enables one of skill in the art to make and use the invention commensurate in scope with the claims without undue experimentation.

As such, Applicant respectfully requests that the claim rejections under Section §112, ¶1, be withdrawn.

III. THE CLAIM REJECTIONS UNDER 35 U.S.C. § 102 SHOULD BE WITHDRAWN

Claims 1, 5, 7-12, 14-15, 27 and 35 are rejected under 35 U.S.C. § 102(b) ("Section 102(b)") as allegedly being anticipated by U.S. Patent No. 5,830,708 ("Naughton"). For the following reasons, Applicant respectfully disagrees.

"A claim is anticipated only if *each and every* element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2USPQ2d 1051, 1053 (Fed. Cir. 1987) (emphasis added).

Naughton discloses a method for producing a secreted human extracellular matrix material by culturing stromal cells on a biocompatible three-dimensional framework *in vitro* (see Naughton, Abstract). In particular, Naughton discloses a method for producing a decellularized extracellular matrix material by (1) isolating stromal cells from a body tissue (see Naughton, col. 5, lines 48-54); (2) growing the stromal cells on a biocompatible three-dimensional framework (see Naughton, col. 5, lines 44-46; col. 9, lines 50-53); (3) allowing the stromal cells to synthesize and deposit on the three-dimensional framework a human extracellular matrix as produced in normal human tissue (see Naughton, col. 6, lines 1-6; col. 9, lines 53-54); (4) killing the stromal cells after secretion of a desired amount of extracellular matrix onto the three-dimensional framework (see Naughton, col. 11, lines 62-67); and (5) removing the killed cells and any cellular debris from the three-dimensional framework (see Naughton, col. 12, lines 1-3).

The claimed methods use a different starting material than that used in the methods of Naughton, and thus, are different than the methods of Naughton. In particular, Naughton uses and conditions stromal cells and a biocompatible three-dimensional framework to create a stromal tissue *in vitro* (see Naughton, col. 5, lines 33-38; col. 6, lines 46-48), whereas the presently claimed invention uses native body tissue. In other words, the decellularized extracellular matrix material isolated by Naughton is prepared using extracellular matrix material produced by a stromal tissue created *in vitro*. In contrast, the decellularized extracellular matrix material isolated by the presently claimed invention is prepared using extracellular matrix material produced by a body tissue created *in vivo*. Since the objective of Naughton is to create *in vitro* tissue matrix systems that mimic those *in vivo*, Naughton fails to teach or suggest the use of native body tissue from a donor body, as recited in claims 1, 27 and 35. As such, Naughton fails to teach or suggest the methods of claims 1, 27 and 35.

Claims 5, 7-12 and 14-15 are dependent on claim 1 and thus, incorporate the limitations of claim 1. As such, Naughton also does not anticipate claims 5, 7-12 and 14-15.

Claim 35 is novel over Naughton for the additional reason that Naughton fails to teach or suggest forming a tissue regeneration scaffold using the decellularized extracellular matrix material, as recited in claim 35. Instead, the decellularized extracellular matrix material of Naughton is further processed with a pharmaceutically acceptable aqueous carrier and placed in a syringe for injection into tissues (see Naughton, col. 5, lines 63-67). Naughton never mentions a tissue regeneration scaffold. As such, claim 35 is further novel over Naughton.

For the foregoing reasons, Applicant respectfully submits that the claim rejections under Section 102(b) are in error and should be withdrawn.

IV. THE CLAIM REJECTIONS UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

Claims 1, 13, 27 and 30 are rejected under 35 U.S.C. § 103(a) ("Section 103(a)") as allegedly being unpatentable over Naughton in view of International Publication No. WO 98/39035 ("Herlyn"). For the following reasons, Applicant respectfully disagrees.

A finding of obviousness under 35 U.S.C. § 103 requires a determination of the scope and the content of the prior art, the differences between the invention and the prior art, the level of the ordinary skill in the art, and whether the differences are such that the claimed subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere*, 383 U.S. 1 (1966). The relevant inquiry is whether the prior art suggests the invention, and whether one of ordinary skill in the art would have had a reasonable expectation that the claimed invention would be successful. *In re O'Farrell*, 853 F.2d 894, 902-4 (Fed. Cir. 1988); *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Both the suggestion of the claimed invention and the expectation of success must be in the prior art, not in the disclosure of the claimed invention. *In re Dow Chemical Co.*, 5 USPQ2d 1529 (Fed. Cir. 1988). In determining obviousness, "the inquiry is not whether each element existed in prior art, but whether the prior art made obvious the invention as a whole for which patentability is claimed." *Hartness International Inc. v. Simplimatic Engineering Co.*, 819 F.2d 1100, 2 USPQ2d 1826 (Fed. Cir. 1987).

Herlyn discloses a method for repairing defects and inducing vascularization in mammalian tissue by administering to the tissue a recombinant replication defective virus carrying a selected growth factor gene under operative control of regulatory sequences which direct the expression of the growth factor (see Herlyn, Abstract). Herlyn does not teach or

suggest decellularizing a conditioned native body tissue to obtain a decellularized extracellular matrix material, as recited in step (d) of claims 1, 27 and 35.

As discussed above, Naughton does not teach or suggest extracellular matrix material that is produced by a native body tissue. Herlyn does not cure the deficiency of Naughton. In fact, there is no suggestion or motivation in either Naughton or Herlyn to modify the reference or to combine the reference teachings. Although both Naughton and Herlyn relate to tissue repair, Naughton uses injection syringes to directly administer the desired amount and type of biological material-containing extracellular matrix material into the target site, whereas Herlyn uses gene therapy to (hopefully) express the desired amount and type of biological material into the relevant target site. The two techniques are different and not interchangeable. As such, there is no motivation to combine or modify the two teachings.

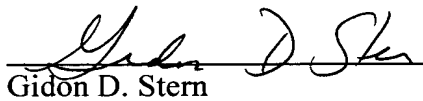
Therefore, Naughton or Herlyn, neither alone or in combination, teaches or suggests the present invention. As such, Applicant respectfully requests that the claim rejections under Section 103(a) be withdrawn.

CONCLUSION

Applicant respectfully requests entry of the amendments and remarks made herein into the file history of the present application. Withdrawal of the Examiner's rejections and an allowance of the application are earnestly requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

Date: February 21, 2006



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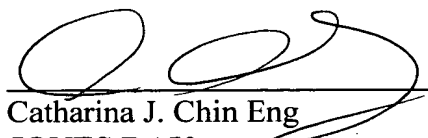
By: 

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